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| EXAMINER | |
|---|---|
| RAO, MANJUNATH N | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

DATE MAILED: 11/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/282,879 | CHATTERJEE, SUBROTO | |
| | Examiner | Art Unit | |
| | Manjunath N. Rao, Ph.D. | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *13,15-17 and 32-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13, 15-17, 32-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claims 13-17, 32-37 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 5-30-06, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Examiner has withdrawn the previous rejection under 35 U.S.C. 112, 2nd paragraph in view of claim amendments.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13, 34 and claims 15-17 and 35-37 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13 and 34 recite the phrase "having **an** amino acid sequence SEQ D NO:2". In doing so, it is now not clear to the Examiner whether applicants mean that said neutral sphingomyelinase comprises the full length of amino acids of SEQ D NO:2 or partial sequences of SEQ ID NO:2. It appears that applicants intend to claim the use of an enzyme comprising the full length of SEQ ID NBO:2. Therefore, Examiner requests applicants to amend the claim to recite "having the amino acid sequence of SEQ ID NO:2". Examiner is aware that he inadvertently suggested amending the claim to recite the phrase "having **an** amino acid sequence SEQ D NO:2" in his previous Office action which he regrets.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 15-17, and 32-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder comprising binding a sphingomyelinase cleavage target to a solid support and contacting said solid support with a pharmacological agent and a recombinant neutral sphingomyelinase having the amino acid sequence of SEQ ID NO:2 does not reasonably provide enablement for such a method in which the neutral sphingomyelinase comprises, a) an amino acid sequence of SEQ ID NO:2; b) a fragment comprising 30 , 50 or 70 amino acids of SEQ ID NO:2 having at least about 50% of the neutral sphingomyelinase activity of SEQ ID NO:2; or c)wherein said sphingomyelinase has an amino acid sequence that is at least 70% identical to SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 13, 15-17, and 32-37 are so broad as to encompass a method of use of any variants or mutants of SEQ ID NO:2 comprising a) an amino acid sequence of SEQ ID NO:2; b) a fragment comprising 30 , 50 or 70 amino acids of SEQ ID NO:2 having at least about 50% of the neutral sphingomyelinase activity of SEQ ID NO:2; or c)wherein said sphingomyelinase has an amino acid sequence that is at least 70% identical to SEQ ID NO:2, for identifying a compound useful in diagnosis or treatment of human sphingomyelinase disorder. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of sphingomyelinases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence to obtain the desired activity requires a knowledge of and guidance with regard to which specific amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single sphingomyelinase having the amino acid sequence SEQ ID NO:2. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides with said function/activity. The specification is limited to teaching the use of SEQ ID NO: 2 as a sphingomyelinase but provides no guidance with regard to the making of variants, mutants, derivatives or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides for use in the above claimed method, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The

Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to make and use the full scope of the polypeptides for the method encompassed by this claim.

While recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, the positions (i.e., amino acid residues) within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompasses the making and using of all polypeptides derived from SEQ ID NO:2 wherein said variants or mutants of SEQ ID NO:2 comprise 30, 50 or 70 amino acids of SEQ ID NO:2 and wherein said variants have at least 50% activity of the sphingomyelinase comprising SEQ ID NO:2 or the making and using of all polypeptides having 70% amino acid sequence identity with SEQ ID NO:2 (i.e., amino acid sequence with 70% identity to the enzyme of SEQ ID NO:2) because the specification does not establish: (A) regions of the protein structure which may be modified without affecting sphingomyelinase activity; (B) the general tolerance of sphingomyelinases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue in SEQ ID NO:2 with an expectation of obtaining the desired biological

function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including sphingomyelinases with an enormous number of amino acid modifications for use in the claimed method. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of sphingomyelinases required for the above method having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action applicant has traversed the above rejection. Applicant argues that the instant invention is enabled as claimed because the specification provides examples of suitable neutral sphingomyelinase species for use with the claimed invention that including fragments thereof. Applicant also argues that the specification provides more than ample guidance towards selecting an appropriate fragment or derivative for use in a particular purpose. Applicant argues that the deduced amino acid sequence of human neutral sphingomyelinase, including key modification and phosphorylation sites (Figure 2) has been provided. Applicant argues that conventional recombinant methods for producing suitable human neutral sphingomyelinase, defined fragments of human neutral sphingomyelinase and an assay to determine the activity of said fragments through measurement of activity with 14C-sphingomyelin, have all been provided in the specification. Examiner respectfully disagrees

with all the above arguments to be persuasive to overcome the rejection. This is because, none of the above arguments attest to "specific guidance" for making and using all the variants encompassed in the claims.

Applicant next, submits that human neutral sphingomyelinase fragments with particular amino acid substitutions are disclosed at least at page 9, lines 1-20, for example, along with details of functional domains of human neutral sphingomyelinase, (specification pages 10-11) and therefore the instant disclosure provides ample description for one skilled in the art to carry out the methods as claimed. Examiner respectfully disagrees with such an argument. This is because a perusal of page 9, lines 1-20 (reproduced below) provides only a general guidance and is extremely weak on specific guidance for making the variants as claimed. It can be seen

> **An N-SMase fragment or derivative of the invention may be (i) a peptide in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) a peptide in which one or more of the amino acid residues includes a substituent group, or (iii) a peptide in which the mature protein is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol). Thus, an N-SMase fragment or derivative includes a proprotein which can be activated by cleavage of the proprotein portion to produce an active mature polypeptide.**

from the passage above that it lacks information as to which specific amino acids in SEQ ID NO:2 can be substituted, deleted or added with which specific amino acid from among the twenty natural amino acids such that the polypeptide continues to have the sphingomyelinase activity. With reference to testing each and every variant made for the specific activity, applicant argues that the specification provides more than ample guidance for selecting an

appropriate active fragment or derivative and as such, any testing needed to identify or confirm suitable human neutral sphingomyelinases or fragments thereof for use in the claimed methods is well within the level of experimentation permitted by the Federal Circuit (*In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Applicant maintains that one of skill in the art having read Applicant's disclosure would know to identify suitable human neutral sphingomyelinases and fragments thereof. Here again Examiner respectfully disagrees. First of all it must be recognized that applicant does not disclose or describe all those sequences that a) a sphingomyelinase comprising an amino acid sequence of SEQ ID NO:2; b) a sphingomyelinase comprising a fragment comprising 30 , 50 or 70 amino acids of SEQ ID NO:2 having at least about 50% of the neutral sphingomyelinase activity of SEQ ID NO:2; or c)wherein said sphingomyelinase has an amino acid sequence that is at least 70% identical to SEQ ID NO:2. even though the specification does general guidelines for making variants. Furthermore, while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants for use in the method as claimed by applicants requires that one of ordinary skill in the art know or be provided with highly specific guidance for making those variants and the selection of which of the infinite number of variants have the claimed property (i.e., sphingomyelinase activity). Thus, for example, in order to make polypeptides which are 70% identical to SEQ ID NO:2, for use in the claimed method, one skilled in the art has to modify up to approximately 30% of the amino acids of the sequence of SEQ ID NO:2, comprising 397 amino acids. As noted in the Office action, the polypeptide variants encompass those having a single amino acid substitution, addition, deletion, or insertion and any combination of amino acid substitutions, additions,

deletions, and/or insertions. Although the claims are not limited to variants having only a single amino acid substitution, in order to generate for example, only single amino acid variants of each amino acid of SEQ ID NO:2, one must make $19^{397}$ variants– just for *single amino acid variants*. Thus, at a minimum, the number of variants is $19^{397}$ and the number becomes seemingly infinite when one considers that the claims broadly encompass simultaneous other alterations by substitution, addition, deletion, and/or insertion. Therefore, while methods to produce variants of a known sequence, e.g., site-specific mutagenesis and random mutagenesis, are well-known to the skilled artisan, producing variants for use in the claimed method requires that one of skill in the art know or be provided with guidance for the selection of which of the at least $19^{397}$ variants has the desired activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the at least $19^{397}$ possible variants. The art clearly *does not* typically engage in the screening of $19^{397}$ single amino acid variants and it follows that the art does not typically engage in the screening of $>19^{397}$ variants to isolate those relatively few variants that would have the desired activity. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As such, based on a determination by weighing all of the factual considerations of *In re Wands*, the examiner has made a determination that the specification does not enable the claimed invention without undue experimentation. Hence the above rejection is maintained.

Claims 13 and 15-17, 32-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13 and 15-17, 32-33, are directed to a method of use of sphingomyelinase polypeptide comprising either an amino acid sequence of SEQ ID NO:2 or fragments of 30, 50 or 70 amino acids of SEQ ID NO:2 and having at least 50% activity of SEQ ID NO:2. Claims 13 and 15-17, 32-33 are rejected under this section of 35 USC 112 because the claims are directed to a method of use of a genus of polypeptides derived from SEQ ID NO:2 including modified polypeptide sequences, (i.e., comprising any 30, 50 or 70 amino acids of SEQ ID NO:2) that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:2 has been provided by applicants which would indicate that they had possession of the genus of polypeptides for use in the claimed method. The specification does not contain any disclosure of the structure of all the polypeptide sequences comprising fragments of 30, 50 or 70 amino acids of SEQ ID NO:2 and having at least 50% activity of SEQ ID NO:2, within the scope of the genus for use in the claimed method. The genus of polypeptides for use in the claimed method is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species (i.e., SEQ ID NO:2) of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus.

Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Applicant has not made any arguments with respect to the above rejections. Therefore, the above rejection is maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13, 15-17 and 32-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chatterjee et al. (J. Biol. Chem., 1989, Vol. 264(21):12554-12561), Ausubel et al. (Current Protocols in Molecular Biology, John Wiley and Sons, 1987, pages 10.0.3-10.0.6).
Ogita et al. (WO 9518119, 7-6-1995) and Taki Takao et al. (Anal Biochem., Jan. 1995, Vol. 224:490-493, cited in the IDS) or Malmqvist, et al.1981 (Zentralblatt fuer Bakteriologie, Mikrobiologie und Hygiene, Abteilung 1, Supplemente (1981), 10(Staphylococci Staphylococcal Infect.), 253-9). Claims 13, 15-17 and 32-37 in this instant application are drawn to a method of identifying a compound comprising binding sphingomyelinase cleavage target (such as sphingomyelin) to a solid support, contacting the solid support with or without a candidate

agent and a recombinant sphingomyelinase enzyme comprising SEQ ID NO:2, followed by incubating under conditions whereby the sphingomyelinase cleaves the cleavage target to yield a product and the presence of the cleavage product is detected and compared between the two reactions, wherein a reduced concentration of the cleavage product relative to the control mixture that does not contain the agent identifies the candidate agent as a compound potentially useful in the treatment of human neutral sphingomyelinase related disorder.

Chatterjee et al. teach an assay method for the activity of neutral sphingomyelinase wherein a mixture of sphingomyelin is treated with the enzyme sphingomyelinase under conditions wherein the substrate is cleaved and cleaved product, ceramide is detected (see page 12555, 2nd column). Chatterjee et al. also teach that sphingomyelinase catalyzes the hydrolysis of sphingomyelin to ceramide and phosphorylcholine at both acidic and neutral pH. The reference also teaches that the study of neutral sphingomyelinases are necessary in view of its involvement in gentamicin-mediated nephrotoxicity in man and also due to the involvement of sphingosine, released as a consequence of the action of sphingomyelinase, in a cascade of reactions leading to the regulation of protein kinase C activity (see page 12554, Introduction). Thus it appears that the substrate, cleavage product and the importance of the sphingomyelinase reaction was common knowledge in the art. However, while the above reference teaches a purified SM and an assay for its activity, it does not teach a recombinant SM or the use of recombinant SM in an assay for detection of a pharmacological agent as claimed above even though the activity assay for the purified enzyme could be used for the same.

Ogita et al. teach the manufacture of a sphingomyelinase inhibitor obtained from a microorganism and its use to treat a variety of diseases and disorders such as HIV, diabetes,

leukemia, cachexia etc. Ogita et al. also teach an assay for determining the inhibitory activity of a compound using sphingomyelinase isolated from a rat brain wherein the assay is performed at a pH of 7.5 very close to the neutral pH. However, both the above references do not teach step of binding the cleavage target to a solid support or the use of recombinant SM.

Takao et al. specifically teach an assay for determining the activity of sphingomyelinase by immobilizing the cleavage target of the enzyme, namely, sphingomyelin, on to a solid support, a membrane followed by contacting the immobilized target with the sphingomyelinase enzyme and determine the cleaved product and correlate it to the activity of the enzyme. However, this reference also does not teach as to how to use the same assay for identifying compounds which modulate the activity of the enzyme.

Malmqvist et al. teach a method of assaying sphingomyelinase activity by using immobilized sphingomyelin on a solid support. The reference teaches the immobilization of the target on to octyl-Sepharose gel support and that stock gel of the immobilized lipid substrate could be stored for months and was easy to handle as a water suspension. However, this reference also does not teach how to use the same assay for identifying compounds which modulate the activity of the enzyme.

With the purified SM as taught by Chatterjee et al. and the knowledge existing in the art of protein biochemistry and molecular biology to make recombinant proteins as provided by Ausubel et al. and the importance of sphingomyelinase inhibitors as taught by Ogita et al., it would have been obvious to one skilled in the art at the time the invention was made to use the purified protein of Chatterjee et al., obtain a cDNA clone and make recombinant sphingomyelinase using the techniques of Ausubel et al. and use it to develop a method of

identifying other compounds which inhibit sphingomyelinase on line with the method of Takao et al. or Malmqvist et al. such that compounds identified could become useful in diagnosis or treatment of a human neutral sphingomyelinase related disorder. Chatterjee et al. teach that one of ordinary skill in the art would be motivated to do this in order to study the biochemical mechanisms involved in gentamicin-mediated nephrotoxicity or in Niemann-Pick disease and Ogita et al. teach that one of ordinary skill in the art would be motivated to do this because, when the transmission of signals introduced by IL-1ß and TNF- α are blocked by inhibiting the activity of sphingomyelinase using an inhibitor, the symptoms of various diseases related to cytokines can be improved. One would have a reasonable expectation of success since Chatterjee et al. provide a purified sphingomyelinase and Ausubel et al. provide time tested recombinant techniques that has been used by a number of other inventors. In addition Takao et al. or Malmqvist et al. provide a robust and time tested assay method wherein the cleavage target is immobilized on a solid support for ease of separation of cleaved products and Ogita et al. demonstrate the existence of a chemical compound which inhibits sphingomyelinase and their importance.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

Arguing against the above rejection applicant maintains that the references do not render the claims obvious. Applicant argues that neither Chatterjee et al., nor Takao et al. or Malmqvist et al. teach a recombinant sphingomyelinase and therefore claims are not rendered obvious. Applicant also argues, when considered as a whole, the references provide no desirable suggestion to combine the teachings and render the instant invention obvious and therefore the

claims as they currently stand are novel over this combination of references. Examiner respectfully disagrees. Examiner also reminds applicant that the above rejection is an obviousness rejection and there is no requirement that each and every reference used must teach the recombinant sphingomyelinase. It is the combination of the teachings of all the references plus what is already known in the art that renders the claims obvious. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Chatterjee et al., Takao et al. or Malmquist et al. all provide the required enzyme and the techniques while Ogita et al. teach the use of an inhibitor of sphingomyelinase which would motivate one of ordinary skill in the art to pursue the above claims.

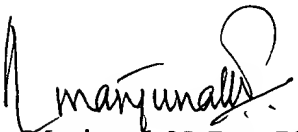
Applicant's argument pointing the various differences between the natural and recombinant enzymes such as (1) the natural enzyme has tightly associated proteases and phosphatases; (2) has an associated (and unwanted) protease activity and (3) the natural enzyme is different from the recombinant version by virtue of being more stable, is also not persuasive to overcome the rejection. This is because such differences appear to be inherent characteristics not detected in the reference of Chatterjee et al. Furthermore while applicant argues that the Chatterjee reference does not suggest or provide any motivation to use a recombinant human sphingomyelinase in any method or process, Examiner maintains that such motivation is

provided by the references of Ogita et al. and others. Examiner has used the Ausubel et al. reference only to show the prevalent knowledge in recombinant technology existing at the time this application was filed. Applicant's argument that Ausubel et al. does not provide any motivation is a highly misplaced argument. For all the above reasons, Examiner continues to maintain the above rejection.

***Conclusion***

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned, is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

October 30, 2006